PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 May 2000 (08.05.00)	
International application No. PCT/GB99/03019	**Applicant's or agent's file reference** DE/PCT131/44134
International filing date (day/month/year) 10 September 1999 (10.09.99)	**Priority date** (day/month/year) 10 September 1998 (10.09.98)
Applicant ALONSO, Carlos Martinez et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

10 April 2000 (10.04.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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C12N 15/12, C07K 14/47, C12N 15/63, C07K 16/18, C12Q 1/68, A61K 38/17, 48/00

A1

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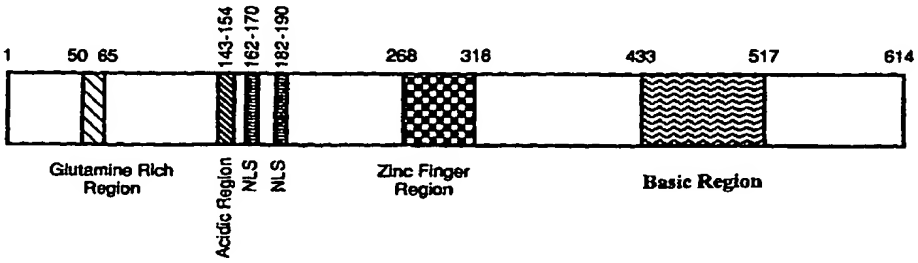
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: GENES ENCODING FOR THE HUMAN AND MURINE DEATH INDUCER-OBLITERATOR-1



(57) Abstract

The present invention relates to a novel DNA sequence that codes for expression of a human Death Inducer-Obliterator 1 (DIO-1)gene and the polypeptide derived from the DNA sequence. Expression vectors containing such sequences and host cells transformed with such expression vectors are also disclosed, as are methods for the expression of the novel DIO-1 polypeptide of the invention, and uses thereof.

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/GB 99/03019

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C07K14/47 C12N15/63 C07K16/18 C12Q1/68
A61K38/17 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K C12Q A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE GENEMBL 'Online! 1 July 1997 (1997-07-01) NAGASE ET AL.: "Human mRNA for KIAA0333 gene, partial cds." XP002130127 Accession No: AB002331 -& NAGASE ET AL: "Prediction of the coding sequences of unidentified human genes. VII. The complete sequences of 100 new cDNA clones from brain which can code for large proteins in vitro." DNA RESEARCH, vol. 4, no. 2, 28 April 1997 (1997-04-28), pages 141-150, XP002102085 --- -/--	1,3,5,6, 8,10-18, 20,21, 27-30

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 February 2000	01/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	ALCONADA RODRIG.., A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter ɔnal Application No
PCT/GB 99/03019

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	DATABASE GENEMBL 'Online! 9 July 1999 (1999-07-09) GARCIA-DOMINGO ET AL.: " Mus musculus mRNA for death inducer-obliterator-1 (Dio-1)" XP002130128 SEQ ID NO: AJ238332 -& GARCIA-DOMINGO ET AL.: "DIO-1 is a novel gene involved in onset of apoptosis in vitro, whose misexpression disrupts limb development." PROC. NATL. ACAD. SCI. USA, vol. 96, no. 14, July 1999 (1999-07), pages 7992-7997, XP002130126 -----	1,3-6, 8-18, 20-30

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

...ernational application No.
PCT/GB 99/03019

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 21-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

Claims 19 (complete), 27 (partially) and 30 (partially)
See FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 19 (complete), 27 (partially) and 30 (partially)

Present claims 19, 27 and 30 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for none of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has not been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the pharmaceutical formulation the polypeptides of the invention (claim 28) and their use as as medicament (claim 29), but it has not been carried out for the compounds which act as agonists or antagonists of the polypeptide of the invention (claim 19), nor for pharmaceutical compositions containing said compounds (claim 28), nor for their use as a medicament (claim 29).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
DGB/PCT131/DE/caw		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/03019	10/09/1999	10/09/1998

International Patent Classification (IPC) or national classification and IPC
C12N15/12

Applicant
CONSEJO SUPERIOR DE INVESTIGACIONES... et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/04/2000	13.03.2001

Name and mailing address of the international preliminary examining authority:

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Authorized officer

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03019

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-11	as originally filed			

Claims, No.:

1-30	as received on	13/09/2000	with letter of	08/09/2000

Drawings, sheets:

1/10,3/10-10/10	as originally filed			
2/10	as received on	13/09/2000	with letter of	08/09/2000

Sequence listing part of the description, pages:

1-7, filed with the letter of 25.01.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☒ furnished subsequently to this Authority in written form.
   - ☒ furnished subsequently to this Authority in computer readable form.
   - ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 19 and 27,28,30 in part.

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 19 and 27, 28, 30 in part .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.
   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;

citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4,7,9,16,17,18, 20-26,28
	No:	Claims	5, 6, 8, 10-15, 27, 29
Inventive step (IS)	Yes:	Claims	1-4,7, 9, 22-26
	No:	Claims	5,6,8,10-18,20,21,27,28,29
Industrial applicability (IA)	Yes:	Claims	1-18, 20, 27, 28,29
	No:	Claims	21-26, see sep. sheet

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. The amended set of claims 1-30, as well as amended Fig. 1B (2/10) are considered to be in conformity with the requirements of Art. 34, 2(b) PCT. Intervening document "PNAS, vol. 96, 7992-7997, Domingo et al." is not considered detrimental to novelty and inventive step of the present application. Said document discloses inter alia the murine nucleotide sequence of 2602 bp length encoding DIO-1. This sequence was already described in the priority documents of 10.09.1998 and 17.09.1998. The priority is thus valid for the murine sequence shown in amended Fig. 1B (2/10) which corresponds to Fig. 1B as originally filed.

2. No search has been carried out for claim 19 (completely) and dependent claims 22, 27, 28 and 30, in part. Therefore, no opinion will be established for claim 19 and claims 22, 27, 28 and 30 insofar as they refer to claim 19 (Rule 66.1 (e) PCT).

3. Claims 21-26 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

   For the assessment of the present claims 21-26 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4. ITEM V

4.1 With respect to document "DATABASE GENEMBL, 01.07.1997, Nagase et al., Human mRNA for KIAA0333 gene, partial cds.", Acc. No. AB002331", claims 5, 6, 8 and 10 to 15 are not considered to be in conformity with the requirements of Art. 33(2), (3) PCT. Claim 5 refers to an isolated DNA fragment not sufficiently precise defined insofar as the parts encoding the N-terminal domain, the C-terminus containing the K-rich region, etc. of the corresponding protein are not determined

in the given nucleotide sequences of Fig. 1A and Fig. 1B (SEQ ID NO.s 1 and 2, respectively). It is noted that the application lacks any indication as to the nucleotide positions denoting the N-terminus and the C-terminus, (i.e. the ORF) of the protein encoded, let alone the starting and ending positions of the particular domains. Fig. E shows the schematic diagramm of the predicted murine DIO-1 ORF on basis of the amino acid sequence, but lacks to indicate the positions determining the N-terminal, the central and the C-terminal part. Moreover, since the human homologue differs from the murine protein, it appears that the positions of the amino acids defining particular motifs may not necessarily correspond. Therefore, the sequence disclosed in Nagase et al. which is identical to SEQ ID NO. 1 with respect to the K-rich C-terminus domain, the Zn finger domain and part of the upstream N-terminal sequence, falls within the scope of claim 5 and dependent claims 12-15.
The same reasoning applies to claims 6 and 8, dependent claim 27 and claims 10 and 11, which lack a sufficiently precise and therefore limiting definition of the term "variants thereof" and of the "nucleic acid probes".

4.2 In view of the above, dependent claims 13 to 17 which inclusively refer to means and methods for recombinant production of DIO-1 variants, dependent claims 18, 20, 21 and 28 which refer to the use of the protein variants to identfy ligands, (anta-)agonists, clones encoding DIO-1, are further not considered to involve particular inventive features according to Art. 33(3) PCT.

5. ITEM VIII

The term Death Inducer-Obliterator 1 (DIO-1) used in the claims is an arbitrary designation introduced by the Applicant. Additional functional features would be necessary to define the protein more precise in the sense of Art. 6 PCT.
The expressions "variants thereof" and "nucleic acid probe" is vague and therefore open to interpretation (claims6 and 8, Art. 6 PCT).

With respect to claim 18 it is noted that the nucleic acid sequences comprised in the expression vector are not referred to the DIO-1 protein. Moreover as already stated above in 4.1, it is not clear whether the amino acid positions denoting the starting and ending points of the particular domains in the mouse protein are

equally valid for the human homologue. Finally, claims 6-9 are directed to a DIO-1 polypeptide but not a DIO-1gene (concerns the part of claim 18 which reads "... interacting with the DIO-1 gene according to ..."), Art. 6 PCT).

Claim 20 appears to be incomplete. Moreover, it is not clear whether the "two-hybrid" method is a method already known and applied in the art (Art. 5 and 6 PCT).
This is also true, for claim 28 which merely refers to "a cell-based reporter assay, transgenic-animal reporter assay or in vitro-binding assay" but fails to define these assays more detailed. Even the description fails to mention at least one example for each of the above assays (Art. 5 and 6 PCT).

The category of claim 29 is unclear. Said claim is directed to a method for identifying a substance and concomittantly refers to the first medical use of the substance. It is noted that in the absence of a clear structural definition of the substance so identified, substances already known in the art to be used for similar purposes are included in the scope of the claim. A first medical use claim is however only allowable with respect to Art. 33(2), (3) PCT, if either the substance is new or a known substance was not previously disclosed for use in treating diseases.

ANNEX

CLAIMS

1. An isolated DNA sequence according to Figure 1A and variants and alleles thereof that codes for expression of the human Death Inducer-Obliterator 1 (DIO-1)gene.

2. A DNA sequence according to claim 1, wherein the DNA sequence is that given in Figure 1A.

3. An isolated DNA sequence according to Figure 1B and variants and alleles thereof that codes for expression of the murine Death Inducer-Obliterator 1 (DIO-1)gene.

4. A DNA sequence according to claim 3, wherein the DNA sequence is that given in Figure 1B.

5. A fragment of an isolated DNA sequence according to any of claims 1 to 4, which encodes for a protein which contains an N-terminal domain, a central non-canonical Zn finger domain, and a C-terminus domain containing a K-rich region.

6. An isolated DIO-1 polypeptide derived from the DNA sequence according to any of claims 1 to 2 comprising the mature human amino acid sequence shown in Figure 1C and variants thereof.

7. A polypeptide according to claim 6 comprising the mature human amino acid sequence shown in Figure 1C.

8. An isolated DIO-1 polypeptide derived from the DNA sequence according to any of claims 3 to 4 comprising the mature murine amino acid sequence shown in Figure 1D and variants thereof.

9. A polypeptide according to claim 8 comprising the mature murine amino acid sequence shown in Figure 1D.

10. A nucleic acid probe for the detection of a nucleic acid sequence encoding a polypeptide according to any of claims 6-9 in a sample.

11. A nucleic acid probe according to claim 10 wherein said probe comprises at least 14 contiguous nucleotides of the sequence given in Figure 1A or 1B.

12. A DNA sequence of any of claims 1 to 5 wherein the isolated DNA comprises a cDNA sequence.

13. An expression vector containing a DNA sequence of any of claims 1-5.

14. A cell transformed with a DNA sequence of any of claims 1-5, such that it allows the direct replication and expression of said DNA sequence.

15. A cell according to claim 14 wherein said cell is a mammalian or a bacterial cell

16. A process for producing a protein according to any of claims 6 to 9 which process comprises the culture of a cell of any of claims 14 to 15 in a suitable culture medium and the isolation of the protein therefrom.

17. A method for identifying clones encoding a DIO-1 polypeptide according to any of claims 6-9, said method comprising screening a genomic or cDNA library with a nucleic acid probe according to any of claims 10 to 11 under low stringency hybridization conditions, and identifying those clones which display a substantial degree of hybridization to said probe.

18. A method of identifying agonists and antagonists of the protein according to any of claims 6-9 comprising transduction or transfection of a mammalian cell line with an expression vector comprising nucleic acid sequences lacking the nuclear localization sequences or lacking the Zn finger domain or lacking the acidic domain or lacking the lysine-rich domain and thereafter identifying the agonist or antagonist interacting with the DIO-1 gene according to claims 6-9.

19. An agonists or antagonists according to claim 18.

20. A method of identifying ligands with which the polypeptide according to any of claims 6-9, interacts, following cloning into and expression in appropriate vectors and using the two-hybrid method.

21. A method to produce specific monoclonal and polyclonal antibodies against the polypeptide according to any of claims 6 to 9 comprising the injection of the polypeptide to a mammalian.

22. Method for treatment of diseases which are characterized by the alteration in cell death or by hyperproliferation, characterized by the administration of compounds according to any of claims 6 to 9 or 19 .

23. Method according to claim 22 by administration of a therapeutically effective amount of the compound.

24. Method according to claim 22 in which the disease is cancer, an autoimmune disease and/or diabetes.

25. Method according to claim 22 in which the disease is rheumatoid artritis, benign and malignant tumors or hyperproliferative skin disorders.

26. Method for treatment of diseases which are characterized in the alteration in cell death or by hyperproliferation, comprising introducing into a mammal a nucleic acid vector according to claim 13 and wherein said nucleic acid vector is capable of transforming a cell *in vivo* and expressing said polypeptide in said transformed cell.

27. A pharmaceutical formulation comprising compounds according to any of claims 6 to 9 or 19 and one or more therapeutically acceptable excipients.

28. A method for identifying a ligand to the compound according to any of claims 6 to 9 or 19, by a cell-based reporter assay, transgenic-animal reporter assay or *in vitro*-binding assay.

29. A method for identifying a substance for treatment of a condition affected by a polypeptide according to any of claims 6 to 9, comprising screening for an agonist or an antagonist of the polypeptide signal transduction to be used for treating metabolic, proliferative or inflammatory conditions.

30. A compound according to any of claims 6 to 9 or 19 for use as a medicament.

FIGURE 1B

tccgtggtag ctctggaaat ggctgcggga tcccggcggc cggggagctt gtttaagagg
cagtccccac tgtccctttg gttgttcgaa gctccggaat cttctcattg atgaactgtg
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aggaaaacct ggggttttcg aagaaccacg attgccaaac gtgagggtgc aggagacacg
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cattcttgtt tcactgctgt acaaggtaca cctttcttac tttttgtaca gtggtttcaa
gtgaattttc atctgtgttc tc

AMENDED SHEET

PATENT COOPERATION TREA

by fax and post

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BANNERMAN, David G.
WITHERS & ROGERS
Goldings House
2 Hays Lane
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442076683550

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	13.03.2001
Applicant's or agent's file reference: DGB/PCT131/DE/caw	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/03019	10/09/1999	10/09/1998

Applicant
CONSEJO SUPERIOR DE INVESTIGACIONES... et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

CORRECTED VERSION!

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Büchler, S Tel.+49 89 2399-8090

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
DGB/PCT131/DE/caw		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/03019	10/09/1999	10/09/1998

International Patent Classification (IPC) or national classification and IPC
C12N15/12

Applicant
CONSEJO SUPERIOR DE INVESTIGACIONES... et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/04/2000	13.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer A. M. Merlos Telephone No. +49 89 2399 8559

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03019

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-11	as originally filed			

Claims, No.:

1-30	as received on	13/09/2000	with letter of	08/09/2000

Drawings, sheets:

1/10,3/10-10/10	as originally filed			
2/10	as received on	13/09/2000	with letter of	08/09/2000

Sequence listing part of the description, pages:

1-7, filed with the letter of 25.01.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No. PCT/GB99/03019

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 19 and 27,28,30 in part.

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 19 and 27, 28, 30 in part .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard:
   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03019

citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4,7,9,16,17,18, 20-26,28
	No:	Claims	5, 6, 8, 10-15, 27, 29
Inventive step (IS)	Yes:	Claims	1-4,7, 9, 22-26
	No:	Claims	5,6,8,10-18,20,21,27,28,29
Industrial applicability (IA)	Yes:	Claims	1-18, 20, 27, 28,29
	No:	Claims	21-26, see sep. sheet

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET International application No. PCT/GB99/03019

1. The amended set of claims 1-30, as well as amended Fig. 1B (2/10) are considered to be in conformity with the requirements of Art. 34, 2(b) PCT. Intervening document "PNAS, vol. 96, 7992-7997, Domingo et al." is not considered detrimental to novelty and inventive step of the present application. Said document discloses inter alia the murine nucleotide sequence of 2602 bp length encoding DIO-1. This sequence was already described in the priority documents of 10.09.1998 and 17.09.1998. The priority is thus valid for the murine sequence shown in amended Fig. 1B (2/10) which corresponds to Fig. 1B as originally filed.

2. No search has been carried out for claim 19 (completely) and dependent claims 22, 27, 28 and 30, in part. Therefore, no opinion will be established for claim 19 and claims 22, 27, 28 and 30 insofar as they refer to claim 19 (Rule 66.1 (e) PCT).

3. Claims 21-26 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

   For the assessment of the present claims 21-26 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4. ITEM V

4.1 With respect to document "DATABASE GENEMBL, 01.07.1997, Nagase et al., Human mRNA for KIAA0333 gene, partial cds.", Acc. No. AB002331", claims 5, 6, 8 and 10 to 15 are not considered to be in conformity with the requirements of Art. 33(2), (3) PCT. Claim 5 refers to an isolated DNA fragment not sufficiently precise defined insofar as the parts encoding the N-terminal domain, the C-terminus containing the K-rich region, etc. of the corresponding protein are not determined

in the given nucleotide sequences of Fig. 1A and Fig. 1B (SEQ ID NO.s 1 and 2, respectively). It is noted that the application lacks any indication as to the nucleotide positions denoting the N-terminus and the C-terminus, (i.e. the ORF) of the protein encoded, let alone the starting and ending positions of the particular domains. Fig. E shows the schematic diagramm of the predicted murine DIO-1 ORF on basis of the amino acid sequence, but lacks to indicate the positions determining the N-terminal, the central and the C-terminal part. Moreover, since the human homologue differs from the murine protein, it appears that the positions of the amino acids defining particular motifs may not necessarily correspond. Therefore, the sequence disclosed in Nagase et al. which is identical to SEQ ID NO. 1 with respect to the K-rich C-terminus domain, the Zn finger domain and part of the upstream N-terminal sequence, falls within the scope of claim 5 and dependent claims 12-15.
The same reasoning applies to claims 6 and 8, dependent claim 27 and claims 10 and 11, which lack a sufficiently precise and therefore limiting definition of the term "variants thereof" and of the "nucleic acid probes".

4.2 In view of the above, dependent claims 13 to 17 which inclusively refer to means and methods for recombinant production of DIO-1 variants, dependent claims 18, 20, 21 and 28 which refer to the use of the protein variants to identfy ligands, (anta-)agonists, clones encoding DIO-1, are further not considered to involve particular inventive features according to Art. 33(3) PCT.

5. ITEM VIII

The term Death Inducer-Obliterator 1 (DIO-1) used in the claims is an arbitrary designation introduced by the Applicant. Additional functional features would be necessary to define the protein more precise in the sense of Art. 6 PCT.
The expressions "variants thereof" and "nucleic acid probe" is vague and therefore open to interpretation (claims6 and 8, Art. 6 PCT).

With respect to claim 18 it is noted that the nucleic acid sequences comprised in the expression vector are not referred to the DIO-1 protein. Moreover as already stated above in 4.1, it is not clear whether the amino acid positions denoting the starting and ending points of the particular domains in the mouse protein are

equally valid for the human homologue. Finally, claims 6-9 are directed to a DIO-1 polypeptide but not a DIO-1gene (concerns the part of claim 18 which reads "... interacting with the DIO-1 gene according to ..."), Art. 6 PCT).

Claim 20 appears to be incomplete. Moreover, it is not clear whether the "two-hybrid" method is a method already known and applied in the art (Art. 5 and 6 PCT).
This is also true, for claim 28 which merely refers to "a cell-based reporter assay, transgenic-animal reporter assay or in vitro-binding assay" but fails to define these assays more detailed. Even the description fails to mention at least one example for each of the above assays (Art. 5 and 6 PCT).

The category of claim 29 is unclear. Said claim is directed to a method for identifying a substance and concomittantly refers to the first medical use of the substance. It is noted that in the absence of a clear structural definition of the substance so identified, substances already known in the art to be used for similar purposes are included in the scope of the claim. A first medical use claim is however only allowable with respect to Art. 33(2), (3) PCT, if either the substance is new or a known substance was not previously disclosed for use in treating diseases.

ANNEX

CLAIMS

1. An isolated DNA sequence according to Figure 1A and variants and alleles thereof that codes for expression of the human Death Inducer-Obliterator 1 (DIO-1)gene.

2. A DNA sequence according to claim 1, wherein the DNA sequence is that given in Figure 1A.

3. An isolated DNA sequence according to Figure 1B and variants and alleles thereof that codes for expression of the murine Death Inducer-Obliterator 1 (DIO-1)gene.

4. A DNA sequence according to claim 3, wherein the DNA sequence is that given in Figure 1B.

5. A fragment of an isolated DNA sequence according to any of claims 1 to 4, which encodes for a protein which contains an N-terminal domain, a central non-canonical Zn finger domain, and a C-terminus domain containing a K-rich region.

6. An isolated DIO-1 polypeptide derived from the DNA sequence according to any of claims 1 to 2 comprising the mature human amino acid sequence shown in Figure 1C and variants thereof.

7. A polypeptide according to claim 6 comprising the mature human amino acid sequence shown in Figure 1C.

8. An isolated DIO-1 polypeptide derived from the DNA sequence according to any of claims 3 to 4 comprising the mature murine amino acid sequence shown in Figure 1D and variants thereof.

9. A polypeptide according to claim 8 comprising the mature murine amino acid sequence shown in Figure 1D.

10. A nucleic acid probe for the detection of a nucleic acid sequence encoding a polypeptide according to any of claims 6-9 in a sample.

11. A nucleic acid probe according to claim 10 wherein said probe comprises at least 14 contiguous nucleotides of the sequence given in Figure 1A or 1B.

12. A DNA sequence of any of claims 1 to 5 wherein the isolated DNA comprises a cDNA sequence.

13. An expression vector containing a DNA sequence of any of claims 1-5.

14. A cell transformed with a DNA sequence of any of claims 1-5, such that it allows the direct replication and expression of said DNA sequence.

15. A cell according to claim 14 wherein said cell is a mammalian or a bacterial cell

16. A process for producing a protein according to any of claims 6 to 9 which process comprises the culture of a cell of any of claims 14 to 15 in a suitable culture medium and the isolation of the protein therefrom.

17. A method for identifying clones encoding a DIO-1 polypeptide according to any of claims 6-9, said method comprising screening a genomic or cDNA library with a nucleic acid probe according to any of claims 10 to 11 under low stringency hybridization conditions, and identifying those clones which display a substantial degree of hybridization to said probe.

18. A method of identifying agonists and antagonists of the protein according to any of claims 6-9 comprising transduction or transfection of a mammalian cell line with an expression vector comprising nucleic acid sequences lacking the nuclear localization sequences or lacking the Zn finger domain or lacking the acidic domain or lacking the lysine-rich domain and thereafter identifying the agonist or antagonist interacting with the DIO-1 gene according to claims 6-9.

19. An agonists or antagonists according to claim 18.

20. A method of identifying ligands with which the polypeptide according to any of claims 6-9, interacts, following cloning into and expression in appropriate vectors and using the two-hybrid method.

21. A method to produce specific monoclonal and polyclonal antibodies against the polypeptide according to any of claims 6 to 9 comprising the injection of the polypeptide to a mammalian.

22. Method for treatment of diseases which are characterized by the alteration in cell death or by hyperproliferation, characterized by the administration of compounds according to any of claims 6 to 9 or 19 .

23. Method according to claim 22 by administration of a therapeutically effective amount of the compound.

24. Method according to claim 22 in which the disease is cancer, an autoimmune disease and/or diabetes.

25. Method according to claim 22 in which the disease is rheumatoid arthritis, benign and malignant tumors or hyperproliferative skin disorders.

26. Method for treatment of diseases which are characterized in the alteration in cell death or by hyperproliferation, comprising introducing into a mammal a nucleic acid vector according to claim 13 and wherein said nucleic acid vector is capable of transforming a cell *in vivo* and expressing said polypeptide in said transformed cell.

27. A pharmaceutical formulation comprising compounds according to any of claims 6 to 9 or 19 and one or more therapeutically acceptable excipients.

28. A method for identifying a ligand to the compound according to any of claims 6 to 9 or 19, by a cell-based reporter assay, transgenic-animal reporter assay or *in vitro*-binding assay.

29. A method for identifying a substance for treatment of a condition affected by a polypeptide according to any of claims 6 to 9, comprising screening for an agonist or an antagonist of the polypeptide signal transduction to be used for treating metabolic, proliferative or inflammatory conditions.

30. A compound according to any of claims 6 to 9 or 19 for use as a medicament.

ANNEX

FIGURE 1B

tccgtggtag ctctggaaat ggctgcggga tcccggcggc cggggagctt gtttaagagg
cagtccccac tgtccctttg gttgttcgaa gctccggaat cttctcattg atgaactgtg
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cattcttgtt tcactgctgt acaaggtaca cctttcttac tttttgtaca gtggtttcaa
gtgaattttc atctgtgttc tc

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